

## Deep brain stimulation diminishes cross frequency coupling in obsessive compulsive disorder

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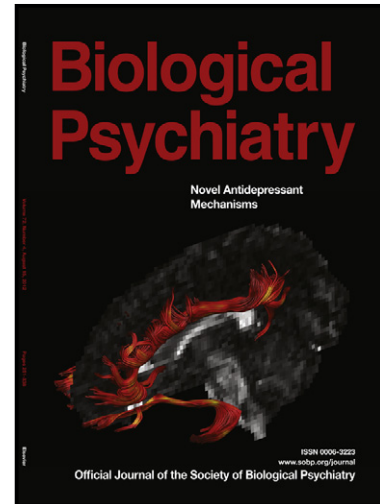
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Deep brain stimulation diminishes cross frequency coupling in OCD

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### **Deep brain stimulation diminishes cross frequency coupling in OCD**

Deep brain stimulation (DBS) has been shown to be an effective treatment for neurological disorders such as Parkinson's disease (PD) (1) as well as psychiatric disorders such as obsessive compulsive disorder (OCD) (2). However, the mechanisms underlying the therapeutic benefits of DBS still remain unclear. A recent ground breaking study has reported that DBS of the basal ganglia in PD patients is able to suppress cross frequency coupling (CFC) between beta phase and broadband gamma amplitude over the motor cortex (3). The authors have speculated that this disruption in cross-frequency interactions in the motor cortex is a mechanism by which DBS of the basal ganglia serves to reduce movement disturbances in PD. Here, we are able to extend on the findings of this study and provide new evidence that the modulatory influence of basal ganglia DBS on cross-frequency neuronal interactions is not limited to the motor cortex of PD patients, but can also be found in the visual cortex of OCD patients.

Attentional biases to threatening stimuli have often been reported in anxiety disorders including OCD (4). Previous work has shown that activity in the basal ganglia can modulate visual attentional switches through fronto-posterior connections (5). Through the same pathway, we hypothesized that alterations in striatal activity through DBS in the ventral internal capsule in OCD patients serves to reduce the bottom-up attentional capacity of the visual cortex such that the amount of information reaching the pre-frontal cortex is reduced. To assess this, we examined EEG data of OCD patients undergoing DBS of the ventral internal capsule. We focused our analyses on the mid-occipital cortex (Oz), which has been shown to demonstrate resting-state CFC in healthy subjects (6). Seven OCD patients that all received the same bilateral stimulation frequency of 130 Hz using the Medtronic Activa PC system were included in this study. All patients were responding positively to the treatment. Two minutes of EEG resting state data (eyes-open) were collected for each patient using an ANT amplifier, with a sampling frequency of 512 Hz, once with DBS 'on' and once with DBS 'off'. The DBS 'on' was followed by a week DBS 'off'. Data was read and preprocessed using FieldTrip (7). To remove line noise, a band-stop Butterworth 4<sup>th</sup> order filter with the frequency bandwidth of 4 Hz was used. Filtered data was re-referenced to the common average across all channels to obtain a better signal to noise ratio and to remove any common activity across all channels. Power spectra were extracted using the Welch method by dividing the 2 minutes into windows of 1 second with a 50% overlap. CFC was assessed based on the coherence between low frequency oscillations and the amplitude envelope of the high frequency oscillations (6). For extracting the high frequency amplitude, six cycles were used. The phase frequency resolution of 0.5 Hz was obtained using the FFT with 1024 time points.

We found that CFC was much stronger over the mid-occipital cortex when DBS was off compared to when DBS was on (see Figure 1A). To compare the CFC values across the two conditions, we averaged the CFC values over a selected window shown in Figure 1A, that is phase frequency between 7 and 40 Hz and amplitude frequency between 60 and 220 Hz for each subject. We used the Kolmogorov-Smirnov test to compare the two values across the two groups. Group analysis confirmed CFC between phase of low frequency oscillations and amplitude of high frequency oscillations was significantly suppressed when DBS was on compared to when DBS was off ( $p=0.0275$ ). As Figure 1A indicates the presence of multiple couplings, we repeated the group analysis with phase frequency in the alpha (8-12 Hz), beta (13-30 Hz), low gamma (30-50 Hz), and high gamma (50-100 Hz) bands. The result showed that only the coupling between the broadband gamma amplitude and phase of beta and low gamma bands were significantly reduced when DBS was on ( $p=0.0275$  and  $p=0.0042$ , respectively). Furthermore, the CFC effect cannot be explained by power as there is no significant difference across the two conditions as can be seen in Figure 1C.

Figure 1 about here.

Previous work in our lab has demonstrated that DBS in OCD patients normalizes the over-connectivity between the nucleus accumbens and prefrontal cortex (8), which we hypothesized to be the result of disruptions of phase-stability of slow rhythms over the prefrontal cortex (9). Phase synchrony has been shown to reflect communication across brain regions (10). In light of these new findings, we propose that DBS improves brain function by dampening neuronal interactions between over-connected

cognitive control networks. The disruption of overall phase synchronization by DBS not only reduces top-down communication from the cortex to the basal ganglia, but also the bottom-up attentional capacity of the visual cortex. These disruptions serve to reduce the disease specific mal-adaptive connectivity within the brain.

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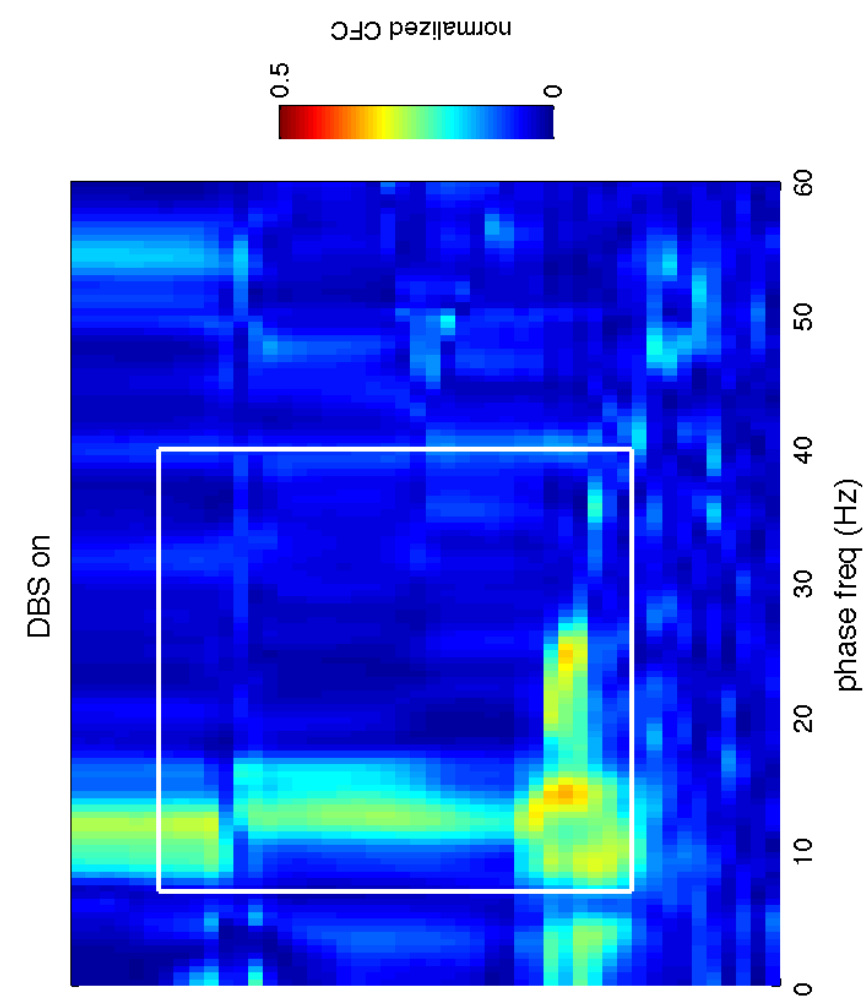
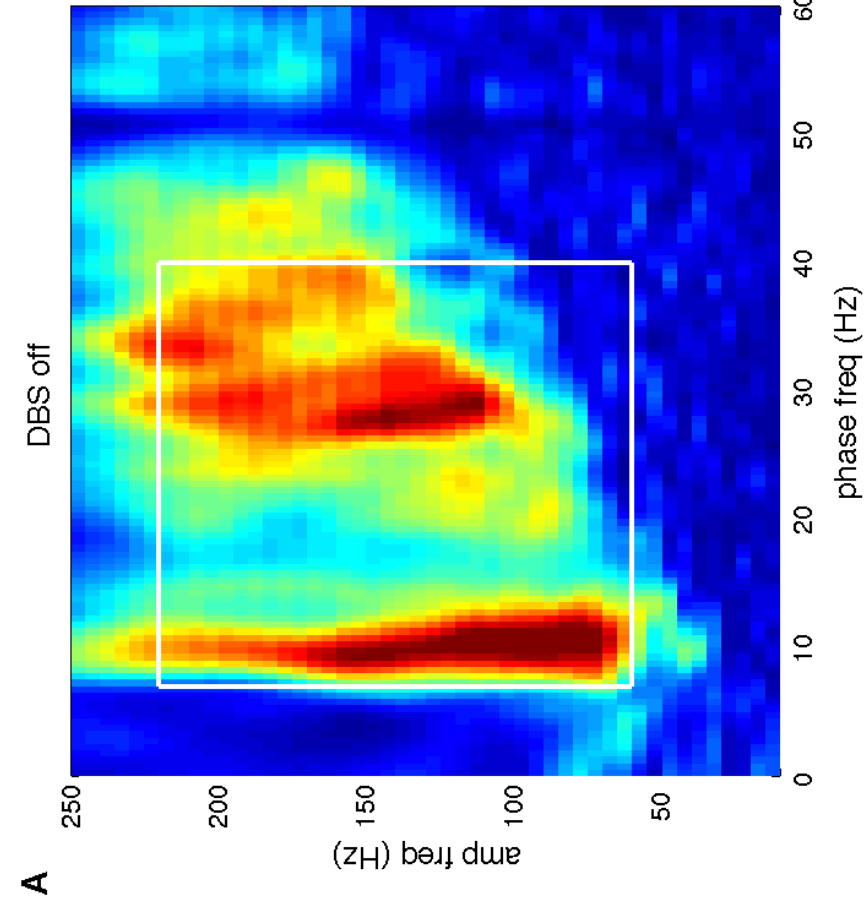
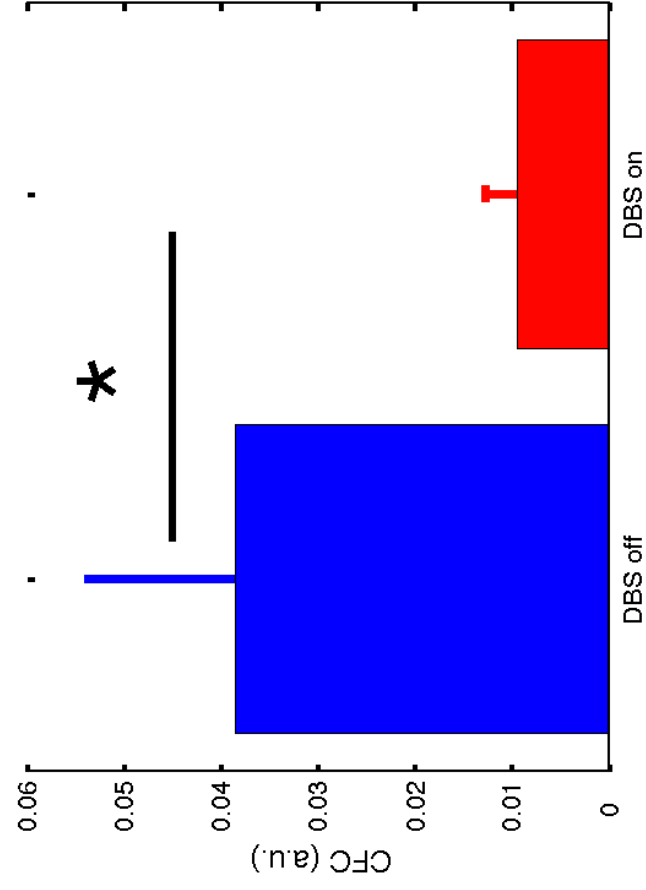
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## Reference:

1. Hammond C, Bergman H, Brown P (2007): Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci.* 30: 357–64.
2. Denys D, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, *et al.* (2010): Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry.* 67: 1061–8.
3. De Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, Starr PA (2015): Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nat Neurosci.* 18: 779–786.
4. Harkin B, Kessler K (2012): Deficient inhibition of return in subclinical OCD only when attention is directed to the threatening aspects of a stimulus. *Depress Anxiety.* 29: 807–15.
5. Van Schouwenburg MR, den Ouden HEM, Cools R (2010): The human basal ganglia modulate frontal-posterior connectivity during attention shifting. *J Neurosci.* 30: 9910–8.
6. Osipova D, Hermes D, Jensen O (2008): Gamma power is phase-locked to posterior alpha activity. (A. Rustichini, editor) *PLoS One.* 3: 7.
7. Oostenveld R, Fries P, Maris E, Schoffelen J-M (2011): FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci.* 2011: 156869.
8. Figee M, Luijckes J, Smolders R, Valencia-Alfonso C-E, van Wingen G, de Kwaasteniet B, *et al.* (2013): Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. *Nat Neurosci.* 16: 386–7.
9. Smolders R, Mazaheri A, van Wingen G, Figee M, de Koning PP, Denys D (2013): Deep brain stimulation targeted at the nucleus accumbens decreases the potential for pathologic network communication. *Biol Psychiatry.* 74: e27–8.
10. Fries P (2005): A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci.* 9: 474–80.

## Figure Legend

Figure 1: CFC as measured in the mid-occipital cortex (Oz) is significantly suppressed when DBS is on. (A) Average CFC values over all patients when DBS is off versus on. CFC values were normalized by the maximum of the window before averaging over patients. The white box shows the window over which we averaged the CFC values to compare the two conditions. (B) Average CFC values over the selected window in panel A with the standard error of the mean over all patients. Significant comparison corresponds to  $p=0.0275$ . (C) Mean together with the standard error of the power spectra over all patients.

**B****C**